UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,326	06/22/2001	George Weiner	C1039/7052 (AWS)	7237

7590 04/18/2006

Alan W. Steele
Wolf, Greenfield & Sacks, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, MA 02210

EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,326	WEINER ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-9,11,14,15,17-21,24,34,43,56 and 78-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-9,11,14,15,17-21,24,34,43,56 and 78-104* is/are rejected.

7)☐ Claim(s) _ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *1/30/06* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 2/2/2006.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claims 1, 7-9, 11, 14, 15, 17-21, 24, 34, 43, 56, 78-104 are currently pending in the application and are addressed herein.

For convenience, it is pointed out that all pending claims except claim 100 are rejected under 35 USC 103 for the reasons of record. The rejections are reiterated herein for convenience. Additionally, claim 100 is now rejected under 35 USC 112, 1st paragraph because the specification has not adequately described the surface antigens which are not expressed on the malignant B-cells prior to CpG oligonucleotide administration but which are expressed on the malignant B-cells after administration of the CpG oligonucleotide.

Interview Summary

A telephone interview was conducted on January 30, 2006 (see attached Interview Summary). During the interview, Applicants indicated that they believed the increased expression of the surface antigens on malignant B-cells was an unexpected result that should obviate the rejection of claims under 35 USC 103. The Examiner indicated that Applicants should submit their arguments in writing. The arguments have been received, and after careful

consideration of the arguments and the rejection of record, Applicants arguments are not found persuasive for the reasons indicated herein.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 7, 8, 10, 11, 14, 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of Winkler et al. (Blood 1999; 94(7), pages 2217-2224; previously cited), for the reasons of record (see Office actions mailed 1/9/03 and 4/20/04), reiterated below for convenience.

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column), which are known to have a low level of CD20 expression, considering neither the claim nor the specification clearly defines what a "low level of CD20 expression" is. The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77). It is noted that although Wooldridge does not specifically indicate that the oligonucleotide administration results in the upregulation expression of a B-cell malignancy surface antigen, Wooldridge does teach administration of 300ug of the oligonucleotide, which is

clearly in the dose range disclosed in the specification (see p. 63 lines 10-15 of the specification, which indicates, "doses of the compounds disclosed herein typically range from about 0.1ug to 10mg per administration"). Therefore, administering the oligonucleotide using the method taught by Wooldridge would necessarily upregulate the expression of a B-cell surface antigen because the effective dose taught by Wooldridge is within the range of efficacy contemplated in the specification (see p. 63, lines 10-15 of the specification).

Wooldridge does not specifically teach that the method can utilizes an antibody specific for a B-cell surface antigen, such as an anti-CD20 antibody, or that the antibody used is specifically C2B8 or Rituximab, or that the oligonucleotide and antibody can be administered together.

Winkler teaches that anti-CD20 antibodies (specifically, Rituximab, which is also referred to as "IDEC C2B8"), can be used to inhibit the growth of B-CLL lymphoma cells which express a low level of CD20. (e.g., see abstract, Figure 1, etc.)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the methods of Wooldridge and Winkler in order to make a method for inhibiting the growth of B-CLL lymphoma cells in a subject having B-CLL lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the Rituximab (IDEC C2B8) antibody taught by Winkler, with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG

ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy.

Furthermore, it would have been prima facie obvious to perform routine optimization to co-administer the oligonucleotide with the antibody at the same time. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that co-administration was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Claims 1, 7, 8, 10, 11, 14, 17-21 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of Winkler et al. (Blood 1999; 94(7), pages 2217-2224; previously cited) and further in view of WO 98/40100 (Davis et al.).

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column), which are

known to have a low level of CD20 expression, considering neither the claim nor the specification clearly defines what a "low level of CD20 expression" is. The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77). It is noted that although Wooldridge does not specifically indicate that the oligonucleotide administration results in the upregulation expression of a B-cell malignancy surface antigen, Wooldridge does teach administration of 300ug of the oligonucleotide, which is clearly in the dose range disclosed in the specification (see p. 63 lines 10-15 of the specification, which indicates, "doses of the compounds disclosed herein typically range from about 0.1ug to 10mg per administration"). Therefore, administering the oligonucleotide using the method taught by Wooldridge would necessarily upregulate the expression of a B-cell surface antigen because the effective dose taught by Wooldridge is within the range of efficacy contemplated in the specification (see p. 63, lines 10-15 of the specification).

Wooldridge does not specifically teach that the method can utilizes an antibody specific for a B-cell surface antigen, such as an anti-CD20 antibody, or that the antibody used is specifically C2B8 or Rituximab, or that the oligonucleotide and antibody can be administered together; nor does Wooldridge teach that the oligonucleotide is ODN 2006 (SEQ ID NO: 729).

Winkler teaches that anti-CD20 antibodies (specifically, Rituximab, which is also referred to as "IDEC C2B8"), can be used to inhibit the growth of B-CLL lymphoma cells which express a low level of CD20. (e.g., see abstract, Figure 1, etc.)

WO 98/40100 (Davis et al.) teaches an immunostimulatory oligonucleotide that is ODN 2006 (i.e., it is 100% identical to SEQ ID NO: 729), which can be used to stimulate B-cell

activation and a therapeutic immune response in a subject (e.g., see the oligonucleotide identified as SEQ ID NO: 6 on page 12 of WO 98/40100, as well as the abstract, paragraph bridging page 1-2, etc.).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the methods of Wooldridge in order to make a the claimed method wherein the SEQ ID NO: 6 oligonucleotide taught by WO 98/40100 is used in combination with the antibody taught by Winkler (Rituximab (IDEC C2B8), with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when an immunostimulatory CpG oligonucleotide is used in combination with a therapeutic tumor-specific antibody a synergistic therapeutic effect is achieved. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy. Furthermore, the oligonucleotide taught by WO 98/40100 is an art-recognized equivalent to the oligonucleotide taught by Wooldridge as both oligonucleotides were recognized as therapeutic immunostimulatory oligonucleotides (See MPEP 2144.06-2144.07).

It also would have been prima facie obvious to perform routine optimization to co-administer the oligonucleotide with the antibody at the same time. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that co-administration was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Claims 1, 7, 9, 10, 14, 17-21 rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of Taji et al. (Japanese Journal of Cancer Research; July 1998; Vol. 89(7), pages 748-756; previously cited) and further in view of Pawade et al. (Histopathology, 1995; 27(2) pages 129-137; previously cited) for the reasons of record (see Office actions mailed 1/9/03 and 4/20/04), reiterated below for convenience.

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column), which are known to have a low level of CD20 expression, considering neither the claim nor the specification clearly defines what a "low level of CD20 expression" is. The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77). It is noted that although Wooldridge does not specifically indicate that the oligonucleotide administration results in the upregulation of CD20 expression, Wooldridge does

teach administration of 300ug of the oligonucleotide, which is clearly in the dose range disclosed in the specification (see p. 63 lines 10-15 of the specification, which indicates, "doses of the compounds disclosed herein typically range from about 0.1ug to 10mg per administration"). Therefore, administering the oligonucleotide using the method taught by Wooldridge would necessarily upregulate the expression of CD20 because the effective dose taught by Wooldridge is within the range of efficacy contemplated in the specification (see p. 63, lines 10-15 of the specification). Furthermore, the oligonucleotide would not hybridize to genomic DNA or RNA under stringent conditions.

Wooldridge does not specifically teach that the method can be used to treat Marginal Zone Lymphoma cells, or using an anti-CD20 antibody (specifically C28B), or that the oligonucleotide and antibody can be administered together.

Taji teaches that anti-CD20 antibodies (specifically, C2B8 antibodies), can be used to inhibit the growth of CD20 positive B-cell lymphoma cells (Specifically, SU-DHL-4 and SU-DHL-6 cells) which express a low level of CD20. Taji teaches that the C2B8 antibodies induce apoptosis in the lymphoma cells which may account for the effectiveness of the C2B8 antibody therapy (e.g., see abstract, etc.).

Pawade teaches that marginal zone lymphoma cells are CD20 positive, indicating that marginal zone lymphoma cells express CD20 antigen.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the methods of Wooldridge and Taji in order to make a method for inhibiting the growth of marginal zone lymphoma cells in a subject having marginal zone lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in

combination with the C2B8 antibody taught by Taji, with a reasonable expectation of success. Since Pawade teaches marginal zone lymphoma cells express CD20 antigen, and since Taji teaches that an anti-CD20 antibody (C2B8) can be used to treat CD20-expressing lymphocytes, there is a reasonable expectation of success

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy.

Furthermore, it would have been prima facie obvious to perform routine optimization to co-administer the oligonucleotide with the antibody at the same time. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that the co-administration was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Claims 1, 7, 9, 10, 14, 15, 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of

Taji et al. (Japanese Journal of Cancer Research; July 1998; Vol. 89(7), pages 748-756; previously cited) and further in view of US Patent 5,969,135 (Ramasamy et al.; previously cited) for the reasons of record (see Office actions mailed 1/9/03 and 4/20/04), reiterated below for convenience.

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column), which are known to have a low level of CD20 expression, considering neither the claim nor the specification clearly defines what a "low level of CD20 expression" is. The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77). It is noted that although Wooldridge does not specifically indicate that the oligonucleotide administration results in the upregulation of CD20 expression, Wooldridge does teach administration of 300ug of the oligonucleotide, which is clearly in the dose range disclosed in the specification (see p. 63 lines 10-15 of the specification, which indicates, "doses of the compounds disclosed herein typically range from about 0.1ug to 10mg per administration"). Therefore, administering the oligonucleotide using the method taught by Wooldridge would necessarily upregulate the expression of CD20 because the effective dose taught by Wooldridge is within the range of efficacy contemplated in the specification (see p. 63, lines 10-15 of the

specification). Furthermore, the oligonucleotide would not hybridize to genomic DNA or RNA under stringent conditions.

Wooldridge does not specifically teach that the method can be used to B-cell lymphoma cells using an anti-CD20 antibody, specifically C2B8, or that the oligonucleotide comprises an amino acid backbone modification, or that the oligonucleotide and antibody can be administered together, or that the oligonucleotide comprises an amino acid modified backbone.

Taji teaches that anti-CD20 antibodies (specifically, C2B8 antibodies), can be used to inhibit the growth of CD20 positive B-cell lymphoma cells (Specifically, SU-DHL-4 and SU-DHL-6 cells) which express a low level of CD20. Taji teaches that the C2B8 antibodies induce apoptosis in the lymphoma cells which may account for the effectiveness of the C2B8 antibody therapy. (e.g., see abstract, etc.)

Ramasamy teaches backbone modifications which can be made on therapeutic oligonucleotides in order to improve certain properties of the oligonucleotide, including increasing their stability towards enzymes. Ramasamy specifically teaches that an amino acid residue modification to the backbone of the oligonucleotide is one such modification (e.g., see column 1, lines 35-60; and column 3, lines 33-45, etc.).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the methods of Wooldridge and Taji in order to make a method for inhibiting the growth of B-cell lymphoma cells in a subject having B-cell lymphoma cells, comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the C2B8 antibody taught by Taji, wherein the oligonucleotide comprises an amino acid modified backbone, with a reasonable expectation of success. Since Ramasamy teaches that the

amino acid backbone modification decreases degradation of the oligonucleotide in vivo, there is a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy.

Furthermore, it would have been prima facie obvious to perform routine optimization to co-administer the oligonucleotide with the antibody at the same time. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that the selection of the source of the nucleic acid, or that co-administration was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Claims 24, 34, 43, 78-81, 83, 84, 86, 90, 91, 94-98, 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously

cited) in view of US Patent 6,306,393 B1 (Goldenberg, previously cited) and further in view of WO 98/40100 (Davis et al.)

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody or that the B-cell malignancy is B-CLL.

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.)

WO 98/40100 (Davis et al.) teaches an immunostimulatory oligonucleotide that is ODN 2006 (i.e., it is 100% identical to SEQ ID NO: 729), which can be used to stimulate B-cell activation and a therapeutic immune response in a subject (e.g., see the oligonucleotide identified as SEQ ID NO: 6 on page 12 of WO 98/40100, as well as the abstract, paragraph bridging page 1-2, etc.).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by WO 98/40100 (specifically the oligonucleotide disclosed as SEQ ID NO: 6 by Davis) in combination with the CD19, CD20, or CD22 antibodies (as taught by Goldenberg), with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when an immunostimulatory CpG oligonucleotide is used in combination with a therapeutic tumor-specific antibody a synergistic therapeutic effect is achieved. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model..." (See page 2997, first column) Thus indicating that immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy. Furthermore, the oligonucleotide taught by WO 98/40100 is an art-recognized equivalent to the oligonucleotide taught by Wooldridge as both oligonucleotides were recognized as therapeutic immunostimulatory oligonucleotides (See MPEP 2144.06-2144.07).

Claims 24, 34, 43, 78-81, 83, 84, 86, 90, 91, 94-99, 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg, previously cited) for the reasons of record (see Office actions mailed on 4/20/04), reiterated below for convenience.

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody or that the B-cell malignancy is B-CLL, or that the specific immunostimulatory CpG oligonucleotide used is ODN 2006 (SEQ ID NO: 729).

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the CD19, CD20, or CD22 antibodies as taught by Goldenberg, with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model..." (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy.

Claims 43, 84-86, 88, 89, 90 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg, previously cited) and further in view of Winkler et al. (Blood 1999, previously cited) for the reasons of record (see Office actions mailed on 4/20/04), reiterated below for convenience.

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody, or that the B-cell malignancy is B-CLL.

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.)

Goldenberg does not teach that the anti-CD20 antibody is Rituximab.

Winkler teaches that anti-CD20 antibodies, and specifically, the anti-CD20 antibody Rituximab, can be used to inhibit the growth of B-CLL lymphoma cells which express a low level of CD20. (e.g., see abstract, Figure 1, etc.) It is noted that Rituximab is an antibody that bind to CD20, thus Rituximab is a specific anti-CD20 antibody.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the CD19, CD20, or CD22 antibodies as taught by Goldenberg. Furthermore, it would have also been prima facie obvious to one of ordinary skill in the art to modify the method to use Rituximab as the anti-CD20 antibody with a reasonable expectation of success since Winkler teaches that Rituximab is an anti-CD20 antibody that can be used to treat B-cell malignancies.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model..." (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy.

Claims 43, 84-86, 88, 89, 90, 91 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg, previously cited) and further in view of Winkler et al. (Blood 1999, previously cited) and further in view of WO 98/40100 (Davis et al.)

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody, or that the B-cell malignancy is B-

CLL, or that the specific immunostimulatory CpG oligonucleotide used is ODN 2006 (SEQ ID NO: 729).

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.)

Goldenberg does not teach that the anti-CD20 antibody is Rituximab.

Winkler teaches that anti-CD20 antibodies, and specifically, the anti-CD20 antibody Rituximab, can be used to inhibit the growth of B-CLL lymphoma cells which express a low level of CD20. (e.g., see abstract, Figure 1, etc.) It is noted that Rituximab is an antibody that bind to CD20, thus Rituximab is a specific anti-CD20 antibody.

WO 98/40100 (Davis et al.) teaches an immunostimulatory oligonucleotide that is ODN 2006 (i.e., it is 100% identical to SEQ ID NO: 729), which can be used to stimulate B-cell activation and a therapeutic immune response in a subject (e.g., see the oligonucleotide identified as SEQ ID NO: 6 on page 12 of WO 98/40100, as well as the abstract, paragraph bridging page 1-2, etc.).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Davis (i.e. SEQ ID NO: 6 of WO 98/40100 which is 100% identical to the instant claimed SEQ ID NO: 729) in combination with the CD19,

CD20, or CD22 antibodies as taught by Goldenberg. Furthermore, it would have also been prima facie obvious to one of ordinary skill in the art to modify the method to use Rituximab as the anti-CD20 antibody with a reasonable expectation of success since Winkler teaches that Rituximab is an anti-CD20 antibody that can be used to treat B-cell malignancies.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy. Furthermore, the oligonucleotide taught by WO 98/40100 is an art-recognized equivalent to the oligonucleotide taught by Wooldridge as both oligonucleotides were recognized as therapeutic immunostimulatory oligonucleotides (See MPEP 2144.06-2144.07).

Claims 43, 84-89, 90 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg, previously cited) and further in view of Winkler et al. (Blood 1999, previously cited) and further in view of Pawade et al. (Histopathology, 1995; 27(2) pages 129-137; previously cited).

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically,

the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody, or that the B-cell malignancy is B-CLL or a marginal zone lymphoma.

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.)

Goldenberg does not teach that the anti-CD20 antibody is Rituximab.

Winkler teaches that anti-CD20 antibodies, and specifically, the anti-CD20 antibody Rituximab, can be used to inhibit the growth of B-CLL lymphoma cells which express a low level of CD20. (e.g., see abstract, Figure 1, etc.) It is noted that Rituximab is an antibody that bind to CD20, thus Rituximab is a specific anti-CD20 antibody.

Pawade teaches that marginal zone lymphoma cells are CD20 positive, indicating that marginal zone lymphoma cells express CD20 antigen.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells wherein B-cell lymphoma is B-CLL or

marginal zone lymphoma, comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the CD19, CD20, or CD22 antibodies as taught by Goldenberg. Furthermore, it would have also been prima facie obvious to one of ordinary skill in the art to modify the method to use Rituximab as the anti-CD20 antibody with a reasonable expectation of success since Winkler teaches that Rituximab is an anti-CD20 antibody that can be used to treat B-cell malignancies. Furthermore, because Pawade teaches that marginal zone lymphoma cells are CD20 positive (e.g., see abstract, etc.), it would have also been prima facie obvious to one of ordinary skill in the art that the method of using CpG oligonucleotide in combination with anti-CD20 antibody could be used to treat marginal zone lymphoma (MZL).

The motivation to make the indicated modification to treat the MZL is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy.

Claims 34, 82, 101, 102 and 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg, previously cited), further in view of Pawade et al. (Histopathology, 1995; previously cited) for the reasons of record (see Office actions mailed on 4/20/04), reiterated below for convenience..

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody, or that the B-cell malignancy is B-CLL or a marginal zone lymphoma.

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.).

Pawade teaches that marginal zone lymphoma cells are CD20 positive, indicating that marginal zone lymphoma cells express CD20 antigen.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the CD19,

CD20, or CD22 antibodies as taught by Goldenberg. Furthermore, because Pawade teaches that marginal zone lymphoma cells are CD20 positive (e.g., see abstract, etc.), it would have also been prima facie obvious to one of ordinary skill in the art that the method of using CpG oligonucleotide in combination with anti-CD20 antibody could be used to treat marginal zone lymphoma (MZL).

The motivation to make the indicated modification to treat the MZL is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy.

Claims 34, 82, 101, 102, 103 and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg, previously cited), further in view of Pawade et al. (Histopathology, 1995; previously cited) and further in view of WO 98/40100 (Davis et al.).

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody,

specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody, or that the B-cell malignancy is B-CLL or a marginal zone lymphoma, or that the immunostimulatory CpG is ODN 2006 (SEQ ID NO: 729).

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.).

Pawade teaches that marginal zone lymphoma cells are CD20 positive, indicating that marginal zone lymphoma cells express CD20 antigen.

WO 98/40100 (Davis et al.) teaches an immunostimulatory oligonucleotide that is ODN 2006 (i.e., it is 100% identical to SEQ ID NO: 729), which can be used to stimulate B-cell activation and a therapeutic immune response in a subject (e.g., see the oligonucleotide identified as SEQ ID NO: 6 on page 12 of WO 98/40100, as well as the abstract, paragraph bridging page 1-2, etc.).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the CD19,

CD20, or CD22 antibodies as taught by Goldenberg. Furthermore, because Pawade teaches that marginal zone lymphoma cells are CD20 positive (e.g., see abstract, etc.), it would have also been prima facie obvious to one of ordinary skill in the art that the method of using CpG oligonucleotide in combination with anti-CD20 antibody could be used to treat marginal zone lymphoma (MZL).

The motivation to make the indicated modification to treat the MZL is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy.

Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; previously cited) in view of Micouin (Leukemia, 1997; previously cited) for the reasons of record (see Office actions mailed on 4/20/04), reiterated below for convenience.

Wooldridge teaches a method of inhibiting the growth of a cancer (B-cell malignancy) wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the cancer. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal

antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach the method can be used to treat cancer using a human or humanized IgG1 isotype antibody.

Micouin teaches that human IgG1 antibodies can be used to treat human leukemia.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Micouin in order to make a method for inhibiting the growth of tumor cells in a subject having the tumor cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the human IgG1 isotype antibodies taught by Micouin, with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy.

112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 100 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 100 explicitly encompasses a surface antigen that is not expressed on the malignant B-cells. The claim is interpreted as meaning that the surface antigen is not expressed on the malignant B cell prior to treatment with the CpG oligonucleotide but after treatment with the CpG oligonucleotide, expression of said surface antigen is upregulated such that the surface antigen is expressed on the malignant B cell. Given the broadest reasonable interpretation, the claim encompasses a genus of surface antigens which are initially not expressed on the malignant B cell, but which are expressed on the malignant B cell after treatment with the CpG oligonucleotide. Looking to the specification for support and guidance, it is clear that the originally filed application contemplated surface antigens not expressed on malignant B-cells prior to CpG administration (e.g., see original claim 34 and page 3), but it does not appear that the specification has identified any specific surface antigens of this genus. For instance, looking to the drawings (especially Figure 3), it appears that all of the surface antigens disclosed were expressed to some degree, even if only in small quantities, in the cells not treated with ODN (see no ODN). Therefore, the claims encompass a genus of surface antigens while the specification does not identify even a single specific species of the genus. It is noted that there are no such surface antigens (i.e., those that are not expressed prior to CpG treatment, but are expressed after CpG treatment) recognized in the prior art.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the specification does not appear to disclose a single species of the claimed genus, nor is there an indication of the distinguishing structural characteristics of the genus of molecules. Accordingly, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the surface antigens encompassed by the claims, therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).)

Response to Arguments

Applicant's arguments filed 2/2/2006 have been fully considered.

With respect to the objection to the specification for including the trademark Rituximab, Applicants argument that Rituximab is not a Trademark is persuasive. Accordingly the objection is withdrawn.

With respect to the rejection of claims 11 and 85 under 35 USC 112, second paragraph for being indefinite since the claims were interpreted as including the trademark/trade name Rituximab, the rejection is withdrawn. Applicants argue that Rituximab is not a trademark or trade name. It is acknowledged that Rituximab is not a trademark. However, Rituximab does meet the definition of a trade name as set forth in MPEP § 608.01(v), which states:

> The expressions "trademarks" and "names used in trade" as used below have the following meanings:
>
> Trademark: a word, letter, symbol, or device adopted by one manufacturer or merchant and used to identify and distinguish his or her product from those of others. It is a proprietary word, letter, symbol, or device pointing distinctly to the product of one producer.
>
> Names Used in Trade: a nonproprietary name by which an article or product is known and called among traders or workers in the art, although it may not be so known by the public, generally. Names used in trade do not point to the product of one producer, but they identify a single article or product irrespective of producer.
>
> Names used in trade are permissible in patent applications if:
> (A) Their meanings are established by an accompanying definition which is sufficiently precise and definite to be made a part of a claim, or
>
> (B) In this country, their meanings are well-known and satisfactorily defined in the literature.
>
> Condition (A) or (B) must be met at the time of filing of the complete application.

In the instant case, Rituximab is not a proprietary word pointing distinctly to the product of one producer. Rather, Rituximab is a generic (nonproprietary) name by which an article or product is known and called among traders or workers in the art. In the instant case, Rituximab is a generic name for a monoclonal antibody specific for CD20 and was known and called such among traders or workers in the art at the time of filing, as evidenced by, for example, Winkler (1999, previously cited) and confirmed by an internet search of the world wide web using the term "Rituximab".

With respect to the rejection of claim 100 under 35 USC 112, first paragraph (new matter), the rejection is withdrawn in view of Applicants' argument that literal support for the limitation could be found on page 3 (lines 11-18 of the specification) and in originally filed claim 34.

With respect to the rejection of claims under 35 USC 103, Applicants arguments have been fully considered but are not persuasive. It is noted that claim 101 was inadvertently omitted from the rejection, but, as previously indicated, Wooldridge teaches that the CpG oligonucleotide comprises a phosphorothioate modified backbone. Accordingly, the rejections which include claim 34 should also include claim 101, as is now the case as set forth above.

Applicants respectfully submit that the claimed feature of upregulation of antigen by CpG is neither taught nor suggested by Wooldridge et al. and that Wooldridge et al. specifically

teaches away from this particular claimed feature because Wooldridge et al. disclose on page 2997 that CpG had no detected effect on the target cells in the model they studied. Applicants contend that Wooldridge et al. teaches instead that immune effector cells, rather than target cells, are affected by CpG oligonucleotide in the particular model they studied. Applicants also assert that none of the additional references cited in combination with Wooldridge et al. teach or suggest the claimed feature of upregulation of antigen by CpG oligonucleotide. Applicants contend that the combination of Wooldridge et al. with any one or more of the additional references cited by the Examiner thus cannot render obvious the claimed subject matter of the rejected claims because no combination of references includes the claimed feature that the cells upregulate expression of an antigen in response to immunostimulatory CpG oligonucleotide.

Applicants respectfully submitted that the enhanced antibody-dependent cellular cytotoxicity (ADCC) reported by Wooldridge et al. relies on ample baseline expression of pertinent antigen by target cells, independent of CpG because had the target cells (unlike the 38C13 cells of Wooldridge et a1.) expressed little or no antigen relevant to the antibody selected for use, and the cells did not upregulate antigen in response to CpG, then the skilled person reading Wooldridge et al. would not have expected immune effector cells to exhibit enhanced ADCC even with CpG oligonucleotide present because there would not be sufficient target antigen to support ADCC.

Applicants argue that the claimed invention is surprising in view of Wooldridge et al., alone or in combination with any of the references cited by the Examiner, because it was previously unknown that CpG can upregulate expression of certain antigens in malignant B cells. Applicants assert that unlike expression by 38C13 cells of antigen recognized by the antibody in

Wooldridge et al., expression of certain antigens by malignant B cells is typically low or absent and can be upregulated in the presence of CpG oligonucleotide and that it would not have been obvious to a person skilled in the art at the time the invention was made to select and use particular antibodies for use in treating B cell malignancies, when the cells of such malignancies express little or no antigen relevant to the particular antibodies, because it was previously unrecognized that CpG can upregulate expression of such antigen by malignant B cells.

In response, Applicants arguments have been fully considered but are not persuasive. It is acknowledged that Wooldridge does not teach that the expression of a surface antigen is upregulated in response to treatment with CpG oligonucleotide. However, Wooldridge does teach treatment of B-cell lymphoma cells (38C13 cells to be exact) with a CpG oligonucleotide. Therefore, although Wooldridge does not recognize that the CpG treatment upregulates expression of surface antigens on the lymphoma cells, the treatment would necessarily result in upregulation of surface antigen expression on the 38C13 cells. Furthermore, Wooldridge does indicate that no direct effect of the CpG ODN was on 38C13 lymphoma cells was detected; however, contrary to applicants assertion that Wooldridge teaches away from this, Wooldridge, also teaches, "[H]owever, it is possible the CpG ODN induced changes in the tumor cells that rendered them more sensitive to MoAb therapy." (See sentence bridging pages 2997-2998). Therefore, rather than teaching away from the CpG ODN having a direct effect on the lymphoma cells, Wooldridge explicitly teaches that such may be the case.

Furthermore, with respect to Applicants argument that no combination of references includes the claimed feature that the cells upregulate expression of an antigen in response to

immunostimulatory CpG oligonucleotide, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). The prior art teaches that immunostimulatory CpG oligonucleotides enhance the efficacy of tumor-specific therapeutic antibodies such that the combination has a synergistic anti-tumor effect (e.g., see Wooldridge et al.). Furthermore, based on the instant disclosure, the immunostimulatory CpG oligonucleotide does not appear to appear to specifically upregulate expression of particular B-cell lymphoma antigens; rather, it appears that the administration of the immunostimulatory CpG oligonucleotides non-specifically increase expression of all B-cell lymphoma surface antigens (e.g., see Figure 3 of the instant Application). Therefore, since the method of treating a B-cell lymphoma using an immunostimulatory oligonucleotide in combination with a anti-tumor antibody that is specific for a B-cell lymphoma surface antigen is prima facie obvious (for the reasons indicated above), and since the amount of immunostimulatory CpG oligonucleotide taught in the prior art (Wooldridge) would necessarily up regulate expression of B-cell lymphoma surface antigens (non-specifically), any anti-tumor antibody specific for a B-cell lymphoma surface antigen (such as RITUXIMAB, etc.) would necessarily be an antibody that is specific for the B-cell lymphoma surface antigen that is upregulated in response to the immunostimulatory oligonucleotide.

Applicants argument that the skilled person reading Wooldridge et al. would not have expected immune effector cells to exhibit enhanced ADCC even with CpG oligonucleotide present because there would not be sufficient target antigen to support ADCC is not persuasive

because Wooldridge teaches that using a CpG ODN in combination with an antitumor antibody results in a synergistic anti-tumor effect. Therefore, although the antigen which the antibody binds may be expressed at a low level, one of ordinary skill would still expect an antitumor antibody (of which there were several effective B-cell specific anti-tumor antibodies known, e.g., Rituximab) to have some effect by itself and to have an synergistically increased effect when used in combination with a CpG oligonucleotide.

Applicants argument that the claimed invention is surprising in view of Wooldridge et al., alone or in combination with any of the references cited by the Examiner, because it was previously unknown that CpG can upregulate expression of certain antigens in malignant B cells is not persuasive because the prior art teaches treating B-cell lymphoma by administering a CpG oligonucleotide in combination with an antitumor antibody and the prior art also teaches specific anti-tumor antibodies which are able to treat B-cell lymphoma (such as Rituximab) thus rendering the claimed method of treatment with the CpG ODN and anti-tumor antibody (such as Rituximab) obvious. Furthermore, administering the CpG ODN would necessarily result in increasing the expression of surface antigens on the malignant B-cells.

Applicants argument that expression of certain antigens by malignant B cells is typically low or absent and can be upregulated in the presence of CpG oligonucleotide and that it would not have been obvious to a person skilled in the art at the time the invention was made to select and use particular antibodies for use in treating B cell malignancies, when the cells of such malignancies express little or no antigen relevant to the particular antibodies, because it was previously unrecognized that CpG can upregulate expression of such antigen by malignant B cells is not persuasive because anti-tumor antibodies which could effectively treat the B-cells

which express little antigen, such as Rituximab were known in the art. Therefore, as long as the cell expresses a tumor antigen that is recognized by the anti-tumor antibody, the antibody would be expected to have some effect, even if only a small effect. Furthermore, based on the teaching of Wooldridge, it would have been prima facie obvious to one of ordinary skill in the art to combine the anti-tumor antibody treatment with administration of CpG ODN because Wooldridge teaches this combination has a synergistic anti-tumor effect and the administration of the CpG would necessarily increase the expression of tumor antigens on the tumor cells. As indicated above, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Therefore, Applicants arguments are not persuasive.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JON ANGELL
PATENT EXAMINER